REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the instant amendments to the claims and drawings and the following remarks.

Claims 12, 19 and 23-27 are pending in the application. Claims 12, 19 and 23-27 are cancelled. Claims 28-34 are added. New claims are redrafted in simplified format and new claim 28 corresponds to cancelled claim 12, claim 29 to claim 19, claim 30 to claim 23, claim 31 to claim24 , claim 32 to claim 25, claim 33 to claim 26 and claim 34 to claim 27. Support for the amended claims can be found throughout the specification. No new matter has been introduced by the instant amendments. Applicants reserve the right to pursue the subject matter cancelled by this or a prior action in this or a subsequent continuation application.

Claims 12, 19 and 23-27 stand rejected under 35 U.S.C. §103(a) as obvious over the Jenuwein et al (US PAT 6555329 B2) in view of Jenuwein et al (US PAT 6689583)

Claims 24-25 and 27 stand rejected under 35 U.S.C. §103(a) as obvious over Kouzarides et al. (WO 02/090578) in view of Jenuwein et al (US PAT 6689583)

Rejection under 35 USC § 103(a)

Claims 12, 19 and 23, 25-26 stand rejected under 35 U.S.C. 103(a) as obvious over Jenuwein et al (US PAT 6555329 B2, hereinafter D1) in view of Jenuwein et al (US PAT 6689583, hereinafter D2) The office action stated as follows:

> Jenuwein et al (US PAT 6689583) suggested the use of SEQ ID NO: 4 to identify modulators of histone methyl transferase and use them to inhibit tumor growth (page 14 paragraph 20-45). Therefore one will motivated to use Jenuwein et al (US PAT 6689583) histone methyl transferase protein of SEQ ID NO: 4 and Jenuwein et al (US PAT 6555329B2) assay method to screen modulators of histone methyl transferase as therapeutic agent for cancer and apoptosis.

The rejection is respectfully traversed.

The claims 28 and 30 (corresponding to former claims 12 and 23 respectively) are specifically directed to methods of screening a preventive or therapeutic agent for breast cancer. The method comprises contacting a protein containing the amino acid sequence of SEQ ID NO: 1 or a salt thereof, S-adenosyl-L-methionine wherein the methyl group is radio-labeled, and histone protein or a polypeptide having the N-terminal sequence of histone H3, with or without a test compound, measuring the radioactivities of histone H3 or polypeptide having the N-terminal sequence of histone H3 by transfer of the methyl group in previous steps, and comparing the level of radioactivities measured in previous step.

The specification of the present application taught and specifically substantiated the methods of screening a preventive or therapeutic agent for breast cancer. For example, in EXAMPLE 1 of the present specification, it was substantiated that SUV39H1 is specifically expressed in the breast cancer tissue (Patient No.6: see TABLE 2). In EXAMPLE 2, it was substantiated that SUV39H1 is not only expressed specifically in the breast cancer tissue, but is engaged in cancer cell growth. On the other hand, neither D1 nor D2 disclosed that an HMTase gene is specifically expressed in cancer tissue, especially breast cancer tissue. Nor was there a disclosure or suggestion that the HMTase gene is involved in breast cancer cell growth. Thus, it is apparent that the present inventors found and substantiated, for the first time, that SUV39H1 is specifically related to breast cancer.

As to claims 29 and 33 (formerly 19 & 26) directed to method of screening an apoptosis inducer, HMTase (SEQ ID NO: 2) described in D1 only has 56% sequence identity with HMTase in D2 (SEQ ID NO: 4: identical to HMTase of the present invention). It is believed that the sequence homology is quite different between these proteins, thus combining the teachings of D1 and D2 would not be able to arrive at the present screening method.

In addition, the applicant would like to bring the Examiner's attention to the declaration under rule 37 CFR 1.132 attached herewith. The applicant actually

screened a compound which inhibits SUV39H1 by using the claimed method. To an assay buffer containing Histone H3 and enzyme solution prepared by the method described in examples 4 and 5 of the specification of the present application, either DMSO (negative control) or Chetomin (a test compound) was added, followed by addition of 3H-S-Adenosyl Methionine. Radioactivity was measured after incubation (paragraph 2.1 in the declaration). Comparison of level of radioactivity was made in figure 2A for the absence (DMSO) and presence of the compound (Chetomin). Figure 2A shows that Chetomin inhibited SUV39H1 effectively in a dose dependent manner (Paragraph 2.2 in the declaration).

The applicant further showed that the screened compound, Chetomin, actually have inhibition effect of the cell growth of MDA-MB-231, which is a human breast cancer cell line used in the experiments described in the declaration. MDA-MB-231 were seeded and cultivated and Chetomin was added thereto. Cell proliferation was analyzed by WST-8 kit (Dojindo, Japan) and apoptosis was analyzed by Cell Death Detection ELISA (Roche) after the addition of Chetomin (paragraph 3.1in the declaration). Figure 5A shows inhibition of the cell growth of MDA-MB-231 by Chetomin and figure 5B shows apoptosis induction by Chetomin (paragraph 3.2 in the declaration). This corroborates that the claimed method of screening works as intended and substantiated in contrast to those described in D1 and D2, both of which were not only quite different (see below) but also either speculative or prophetic.

Further, there are critical differences between HMTase described in D1 and that in D2 as discussed below.

First, it was reported by Jenuwein that tissue distribution of HMTase in D1 was different from HMTase in D2 (Mol Cell Biol. 2000 Dec: 20(24): 9423-33; attached to previous response). Suv39h2 (identical to HMTase in D1) is expressed specifically in testes, while Suv39h1 (identical to HMTase in D2) shows relatively broad expression (Fig. 5A). These data suggest that each of the proteins plays a different role in different cells or tissues.

Second, there is a structural difference between Suv39h2 (D1) and Suv39h1 (D2). Suv39h2 comprises a highly basic N-terminal extension with 82 amino acids,

which is not present in Suv39h1. This difference was also mentioned in the paper (Fig. 1B). It is well accepted by a skilled person that a difference in a protein function depends upon a difference in secondary structure of the protein. Thus, one skilled in the art should recognize that it is hard to predict actual cellular function of Suv39h1 and Suv39h2 and to place Suv39h1 and Suv39h2 in the same class, while both proteins have HMTase activities.

Therefore, there is neither suggestion nor motivation for combining D1 with D2 in these references. It is not believed obvious for a skilled person to use modulators of HMTase obtainable by the assay method in D2 as apoptosis inducer as taught by D1.

Any rejection of a claim for obviousness over a combination of prior art references must establish that (1) the combination produces the claimed invention and (2) the prior art combines a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention (In re Vaek, 947 F.2d 488; 20 USPQ2d 1438-Fed.Cir.1991). In addition, the Examiner's prima facie case must include a finding that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work (In re O'Farrell, 853 F.2d 894, 903-904; USPQ2d 1529, 1531-Fed. Cir. 1988). IN the present office action, the Examiner has not established a prima facie case of obviousness.

Thus, for at least these reasons, claims 28 to 34 (formerly claims 12, 19 and 23, 25-26) are patentable over D1 and D2.

Claims 24-25 and 27 stand rejected under 35 U.S.C. 103(a) as obvious over Kouzarides et al. (WO 02/090578, hereinafter D3) in view of Jenuwein et al (US PAT 6689583, D2) The office action stated as follows:

> Kouzarides et al. teaches methods of screening modulators of histone methyl transferase by measuring the methylated and unmethylated histone polypeptide reacted with s-adenosyl-L-methionine in presence of test compound using MALDI Mass spectrometry (merely an assay method) and suggested the test compound as therapeutic agent for cancer and apoptosis inducer.
>
> Jenuwein et al. suggested the use of SEQ ID NO: 4 to identify modulators of histon methyl transferase and use them to

inhibit tumore growth (page 14, paragraph 20-45). Jenuwein et al. also suggested the use of Mass spectrometry (merely an assay method) to identify modulators Suv 39h (SEQ ID NO: 4 (Page 12 paragraph 12-30).

The rejection is respectfully traversed.

The applicants disagree with the above contention. In D3, mass spectrometry was used for identifying a set of proteins binding to unmethylated H3 peptides, which would be putative components of a binding complex in the context of confirming the specificity of the proteins binding to unmethylated H3 peptides (see, e.g., line 23 in page 48 to line 7 in page 49, line 28 in page 53 to line 14 in page 54 of D3). Here, MALDI mass spectrometry was used for totally different purposes from that of the present application.

Furthermore, Jenuein et al (US 6,689,583 B1, D2) used mass spectrometry to identify new Suv39h substrate, i.e., "equivalent to or mimicking the naturally occurring substrate, e.g., biochemically purified histone H3..." (column 12, lines 17-30).

On the hand, in the present invention, mass spectrometry was used for screening modulators of HMTase (see, e.g., page 30, lines 2-12 of the specification) Thus, it is believed that a skilled person could not have been motivated to combine D2 and D3, to utilize the mass spectrometry for the screening method as disclosed in D2.

Thus, for at least these reasons, claims 31, 32 and 34 (formerly claims 24, 25 and 27) are patentable over D2 and D3.

In view of the foregoing, applicants respectfully request reconsideration, withdrawal of all grounds of rejection and objection, and allowance of claims 28 to 34 in due course.

Respectfully submitted,

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